Variability among institutional review boards' decisions within the context of a multicenter trial

Henry Silverman, MD; Sara Chandros Hull, PhD; Jeremy Sugarman, MD

Background: **Institutional review boards (IRBs) are given discretion to interpret and apply the federal regulations governing the protection of human subjects in research.**

Objective: **To determine the extent of the variability among different IRBs on their approved research practices and informed consent forms within the context of a multicenter trial that used a common protocol.**

Design: **Descriptive analysis of survey information and informed consent forms.**

Setting and Participants: **Sixteen IRBs from the institutions participating in a multicenter trial comparing lower vs. traditional tidal volume ventilation in patients with acute lung injury.**

Measurements: **Analysis of survey information on IRBs' approved research practices. Analysis of informed consent forms for the presence and the adequacy of description of each basic element of informed consent specified in the federal regulations. Reading levels of informed consent forms.**

Main Results: **Surveys and IRB-approved consent forms were obtained from all of the contacted IRBs (n = 16). Variability was observed among several of the research practices; one IRB waived the requirement for informed consent, five IRBs permitted telephone consent, and three IRBs allowed prisoners to be enrolled. Three consent forms contained all of the basic elements of informed consent outlined in the federal regulations, and 13 forms had varying numbers of these elements absent (six forms without one element, four without two, one without three, and two without four). Reading levels of the consent forms ranged from grades 8.2 to 13.4 (mean ± SD was 11.6 ± 1.2 grade level).**

Conclusions: **Within a multicenter trial, IRBs reviewing a common protocol varied in several of their approved research practices and in the extent to which the basic elements of informed consent were included in their consent forms. (Crit Care Med 2001; 29:235–241)**

KEY WORDS: respiratory distress syndrome; adult; informed consent; professional staff committees; bioethics; multicenter studies; human experimentation; clinical protocols; research, standards; research, legislation and jurisprudence

Institutional review boards (IRBs) are responsible for reviewing proposals for research with human subjects to ensure that the research complies with the federal regulations governing the protection of human subjects, including the requirements for informed consent (1, 2). Variability among IRBs regarding their approved research practices can be expected, because IRBs are given discretion in interpreting and applying these regulations. For example, the local setting (such as state laws, institutional policies, professional and community standards, and population differences) can lead appropriately to different decisions among IRBs. In addition, interpreting the regulations often calls for ethical reflection, discretion, and the balancing of the ethical principles that ought to guide the conduct of research: respect for persons, beneficence, and justice (3). Accordingly, IRB members may bring their own interpretive points of view to the review process. Furthermore, the complexity of some research projects can preclude a simplistic application of the federal regulations. IRBs also may decide to adopt standards that are higher than those articulated in the federal regulations. Variability, however, may stem from other sources, such as unintentional ambiguity in the federal regulations, as well as differences in the knowledge of IRB members with respect to the content, intent, and meaning of the federal regulations. Finally, IRBs may differ in the adequacy of their review processes.

One of the many changes that have taken place in the research environment since the inception of the basic federal regulations in 1974 has been the proliferation of multicenter trials and, hence, the review of a common protocol by multiple IRBs (4). The use of a common protocol, simultaneously submitted to several IRBs, affords an opportunity to examine the variability in research practices and in the consent forms approved by different IRBs within the context of the current federal regulations.

METHODS

Multicenter Ventilator Management Clinical Trial

The National Heart, Lung and Blood Institute (NHLBI)-sponsored ARDS Clinical Trials Network (ARDS Network) was formed in 1994 to conduct multicenter trials of new strategies for the treatment of critically ill patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The ARDS Network consists of ten centers, and each center consists of one or more institutions. One of the clinical trials performed by the ARDS Network involved assessing the safety and efficacy of two methods of ventilator management: lower

From the Division of Pulmonary and Critical Care, Department of Medicine (Dr. Silverman), University of Maryland School of Medicine, Baltimore, MD; Bioethics Section, National Human Genome Research Institute (Dr. Hull), National Institutes of Health, Bethesda, MD; and the Departments of Medicine and Philosophy (Dr. Sugarman), Director for the Center for the Study of Medical Ethics and Humanities, Duke University, Durham, NC.

Address requests for reprints to: Henry Silverman, MD, University of Maryland School of Medicine, Division of Pulmonary and Critical Care Medicine, 10 South Pine Street, Baltimore, MD 21201. E-mail: hsilverm@medicine.umaryland.edu

(6 mL/kg) vs. traditional (12 mL/kg) tidal volume ventilation. This ventilator trial has been described in detail elsewhere (5). Investigators had 36 hrs from the onset of ARDS/ALI to obtain informed consent and enroll patients in the study. Once enrolled, subjects were assigned randomly to receive either lower or traditional tidal volume ventilation. The administration of either lower or traditional tidal volume ventilation was considered standard therapy, the selection of which is based typically on the preferences of individual physicians. Mechanical ventilation was not considered to pose additional risks, because patients would have been exposed to some form of ventilation if not enrolled.

Procedures performed solely for research purposes included obtaining an arterial blood gas determination at study entry, venous blood samples (10 mL) at study entry and on days 1 and 3 for measurement of inflammatory mediators, and a urine pregnancy test (pregnancy was an exclusion criterion because the effects of hypercapnea, which may be more likely to occur when lower tidal volumes are used, on the developing fetus are unknown).

A common study protocol (developed by the ARDS Network and approved both by an NHLBI-appointed, independent Protocol Review Committee and a Data Safety and Monitoring Board) and a sample consent form (developed by the ARDS Network's ethics committee and containing all of the basic elements of informed consent delineated in the federal regulations) (6) were provided to each investigator involved in the study for use in preparing their submissions to their local IRBs. The common study protocol could not be altered, but there was no requirement for the investigators to use the sample consent form. All participating institutions had IRB approval to conduct the ventilator trial and used their respective IRB-approved consent forms.

Participating institutions were reimbursed for fixed research-related costs (e.g., investigator, research coordinator, and secretarial support), as well as for incremental costs incurred with the recruitment of subjects. It was anticipated that the investigators at each institution would enroll a certain number of patients per year.

Data Collection

After institutions obtained IRB approval, the IRBs were contacted and asked to complete a survey on their approved research practices for the ventilator trial and to provide a copy of the consent forms approved for use in the trial.

Survey of Approved Research Practices

The survey sent to the IRBs inquired about the following research practices for the ventilator trial: a) waiver of informed consent; b) permissibility of telephone consent; c) allowance of family members to serve as proxy for informed consent; d) participation of prisoners; e) requirement that investigators' financial compensation be stated in the informed consent form; and f) prohibition of investigators who served as the patients' treating physician from obtaining informed consent. These issues were selected, because they have been discussed frequently in various forums (7–13).

Analysis of Informed Consent Forms

Reviewers evaluated each form for the presence of the basic elements of informed consent specified in the federal regulations (6) and assessed the degree to which the language used to describe the elements was complete and/or understandable.

A scale of 1–5 was used to rate each element. A score of 1 indicated that the description of the basic element provided complete and understandable information; a score of 5 reflected that the basic element was not present in the consent form; and scores between 2 and 4 indicated that the basic element was mentioned but contained insufficient content and/or ambiguous language. Initially, two primary reviewers (SCH and JS), who were blinded to the identities of the institutions associated with the consent forms, performed an independent assessment and then rated jointly the degree with which they believed each basic element was addressed in the consent form. The two primary reviewers had expertise in research ethics and knowledge of the federal regulations. This methodology was adapted from a similar consensus-based approach used by the Advisory Committee on Human Radiation Experiments in its empirical review of contemporary federally funded research involving human subjects (14). A third reviewer (HS), a principal investigator in the ventilator trial, was available to answer any questions about the protocol and also examined the consent forms and the ratings to verify any assessment that a basic element was not present in a consent form and to ensure consistency of the ratings between the consent forms. The final ratings for all of the basic elements were decided ultimately by the two primary reviewers.

Reading Levels

Each consent form was scanned optically, checked for accuracy, and analyzed by computer software (Word Perfect for Windows) that used the Flesch-Kincaid formula to determine reading grade levels.

IRB Review

The IRB at the University of Maryland School of Medicine reviewed this study protocol and determined it to be exempt from the IRB approval process.

RESULTS

Of the 23 institutions that had been involved in the ARDS Network, 22 participated in the ventilator trial and made submissions to their local IRBs. One institution began participation in the trial after our surveys were sent to the IRBs, and in five instances, two institutions had the protocol reviewed by the same IRB. Surveys and IRB-approved informed consent forms were returned from all of the contacted IRBs (n = 16).

Approved Research Practices

IRB-approved research practices are shown in Table 1. All IRBs allowed family members to serve as proxy decision-makers, all did not require mention of investigators' financial compensation in the consent form, and all did not prohibit

Table 1. Approved research practices of the institutional review boards (n = 16)

Question	Response		
	Yes	No	Not Answered
1. Waiver of informed consent granted?	1	15	0
2. Telephone consent allowed?	5	10	1
3. Family members allowed as surrogate decision-makers?	16	0	0
4. Prisoners allowed to participate?	3	11	2
5. Disclosure of investigators' financial compensation required in consent form?	0	16	0
6. Treating physician-investigator prohibited from obtaining consent?	0	16	0

investigators who also served as the patients' treating physician from obtaining informed consent. Variability was observed for the other approved research practices. For example, of the 16 IRBs, one waived the requirement for informed consent. According to this IRB, the waiver was justified, because the ventilator trial presented minimal risks to the subjects and satisfied "the standards outlined" in the federal regulations for a waiver of consent. The waiver was allowed only when proxy decision-makers could not be contacted within the 36-hr enrollment window. Afterward, written, signed consent for continued participation was sought from either a proxy decision-maker and/or the subject (if he or she regained decision-making capacity). Five IRBs allowed informed consent to be obtained from the subjects' proxies by telephone. Of the IRBs that allowed telephone consent, one IRB required that signed informed consent be obtained by the next day, another IRB required signed consent on arrival of the subject's representative at the hospital, and another allowed ≤5 days to elapse before obtaining a signed informed consent document from the representative. Two IRBs had no time requirement for obtaining a signed informed consent document. Three IRBs allowed prisoners to participate in the study.

Informed Consent Forms

The extent to which the basic elements of informed consent were included in consent forms is shown in Table 2. Three consent forms contained all of the basic elements, six forms did not include one element of informed consent, four forms did not include two elements, one form did not include three elements, and two forms did not include four elements.

Differences in the descriptions of the basic elements were observed in the consent forms (Table 2). For example, one form contained incomplete information about the risks associated with the ventilatory interventions (". . . for patients receiving 12 ml/kg volumes, the airway pressures will be carefully monitored and not allowed to rise above a certain level"—hence, explicit information about the specific adverse effects associated with high airway pressures was not given). Concerning the potential benefits of participating in the study, four consent forms did not explicitly state that subjects may not receive any direct benefits from participating in the study.

Nine forms contained incomplete information about alternatives to participation, either not stating that standard therapy would be given if patients did not participate in the trial and/or not mentioning explicitly that there are alternative ways of ventilating patients with ARDS/ALI. A description of alternative treatments in one consent form that pro-

Table 2. Variability of information in informed consent forms

Basic Element[a]	No. of Consent Forms, Rating[b] 1	2	3	4	5
Element 1					
a. Purpose of the research	16	0	0	0	0
b. A statement that the study involves research	14	0	2	0	0
c. Expected duration of the subject's participation	16	0	0	0	0
d. Description of the procedures to be followed:					
i) Randomization procedure	14	2	0	0	0
ii) Ventilatory interventions	14	1	1	0	0
iii) Blood sampling and urine pregnancy test	16	0	0	0	0
Element 2					
Description of any reasonably foreseeable risks or discomforts to the subject:					
a. Ventilatory interventions	14	0	1	0	1
b. Blood sampling	9	0	0	0	7
Element 3					
Description of benefits:					
a. To the subject	12	0	4	0	0
b. To others	12	2	0	0	2
Element 4					
Disclosures of alternatives to participation	6	5	4	0	1
Element 5					
Assurances of confidentiality	16	0	0	0	0
Element 6					
For research involving more than minimal risk, if research injury occurs:					
a. An explanation as to whether any compensation is available	14	0	0	0	2
b. An explanation as to whether any medical treatments are available	15	0	0	0	1
Element 7					
a. An explanation of whom to contact for answers to questions about the research	15	0	0	1	0
b. An explanation of whom to contact for questions about the research subjects' rights	13	0	0	1	2
c. An explanation of whom to contract in the event of a research-related injury	12	0	0	2	2
Element 8					
a. Voluntariness of participation	13	0	0	0	3
b. Ability to withdraw	15	0	0	0	1

[a]The number assigned to each element refers to the subparagraph in Section 46.116a of the Code of Federal Regulations where the basic element is mentioned; [b]1, basic element present with complete and understandable information; 5, basic element not present; 2–4, basic element present, but contained insufficient content and/or ambiguous language.

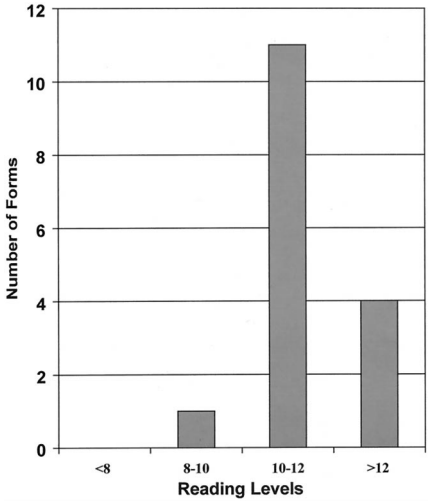

Figure 1. Reading grade levels of informed consent forms.

vided complete information was as follows: "If I decide not to participate in this study, I will receive the standard treatment for my lung injury, which may include the use of fluids, blood pressure medication, and antibiotic therapy to treat infections. Finally, a breathing machine will be used to deliver varying volumes of oxygen-enriched air."

The reading levels of the consent forms are shown in Figure 1; the readability levels ranged from grades 8.2 to 13.4 grade (mean ± SD was 11.6 ± 1.2 grade level).

DISCUSSION

In a multicenter clinical trial involving critically ill patients, we observed variability in the research practices and the content of consent forms approved by local IRBs that reviewed a common protocol. Such variation is not inherently inappropriate, because IRBs are given wide latitude to interpret and apply the federal regulations. We could not determine from this study the reasons for the observed variability, but a discussion of the potential sources of this variability in the context of this ventilator trial may have significance for the review and conduct of other multicenter trials.

One IRB in the multicenter trial granted a waiver of informed consent. Federal regulations allow IRBs to waive the requirement for obtaining informed consent when all of the following criteria are met: "(a) the research involves no more than minimal risk to the subjects; (b) the waiver . . . will not adversely affect the rights and welfare of subjects; (c) the research could not practicably be carried out without the waiver . . .; and (d) whenever appropriate, the subjects will be provided with additional information after participation" (15). The one IRB that granted a waiver of informed consent stated that the clinical trial involved "minimal risks" and met the "standards outlined" in the federal regulations for a waiver. Under federal regulations, minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (16). There have been, however, vigorous debates over the meaning of this definition (7, 17). For example, the phrase "those ordinarily encountered in daily life" begs for the specification of a context: either the daily lives of healthy individuals or of those subjects who have the disease. In addition, the second part of the definition—the risks encountered "during the performance of routine physical or psychological examinations or tests"—gives IRBs the challenging task of figuring out which interventions are encountered ordinarily or are routine in an equally wide variety of clinical settings. For the ventilator trial, it is conceivable the IRB that granted the waiver of consent held that the arterial and venous blood samples obtained as part of the study posed only minimal risks, because such blood samples are collected during "routine physical exams" of subjects requiring ventilatory support. If the different interpretations that have been given to the phrase "minimal risk" are considered inappropriate, then further clarification is warranted from the federal government.

The federal regulations also require that a waiver of informed consent should not adversely affect the rights and welfare of subjects. One could claim that patients or their proxies should have the right to decide to participate in a research study. However, if such an absolute right exists, then any waiver must be construed as depriving subjects of their rights, which would make it impossible to justify any waiver (12). Alternatively, IRBs may require additional protections of the rights of subjects that can justify a waiver. For example, the IRB that granted a waiver of consent permitted the waiver only if the subject's proxy could not be contacted within the 36-hr enrollment window and required signed, written consent for continued participation from the subject's proxy once he or she arrived, and/or from the subject, if she or he regained competence.

The condition that "the research could not practicably be carried out without the waiver" requires a plausible concern that either the findings or the conduct of the research might be impossible or adversely affected by having to obtain informed consent (12). A concern with the delay of the clinical trial because of logistic considerations at the local institution (e.g., if the institution served a large geographic area, hence precluding the timely arrival of the subjects' proxies) might have prompted the IRB to grant a waiver of informed consent. The ventilator trial, however, was a multicenter trial, and hence it is uncertain whether such a waiver can be justified for one institution when the other institutions participating in the trial are able to conduct the research in a timely fashion by enrolling subjects from whom consent or proxy consent can be obtained. In such a situation, it appears then that the research on a national level could "practicably" be carried out without the waiver. However, although the IRB that granted the waiver was aware that other institutions were participating in the ventilator trial, as evidenced by the information contained in that institution's IRB-approved consent form, it is unclear whether the IRB had knowledge of the consent practices of the other institutions or whether the ventilator trial was being conducted in a timely fashion at the national level. Whether a local IRB should consider the practicableness of performing the research in other locations is not addressed in the federal regulations, which were promulgated before multicenter trials proliferated. This issue warrants further clarification from the federal government.

IRBs that allowed a telephone consent process followed by signed confirmation in lieu of a signed informed consent document before enrollment might have done so to accommodate the time constraints of the clinical trial's 36-hr enrollment window (which may not be enough time for some subjects' representatives to be present physically in the hospital to sign the consent form). The federal regulations require the subject or the subject's legally authorized representative to sign either a written consent document (18) or a "short form written consent document" stating that the elements of informed consent have been orally pre-

sented (19). The regulations do provide for exceptions to the requirement for a signed consent form if the IRB "finds either: (a) The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. . . ; or (b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context" (20). Because the first condition was not relevant for the ventilator trial, the latter condition could have been used to justify the waiver of signed, written informed consent. Variable interpretations of this exception by the IRBs might have accounted for the observed differences in their approved practices regarding telephone consent.

Concerning the issue of prisoner participation, under the federal regulations, biomedical or behavioral research "may involve prisoners as subjects only if. . . the proposed research involves solely the following:

(a) study of the possible causes, effects, and processes of incarceration, and of criminal behavior provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
(b) study of prisons as institutional structures or of prisoners as incarcerated persons provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
(c) research on conditions particularly affecting prisoners as a class. . .; or
(d) research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary [of Health and Human Services] has consulted with appropriate experts. . ." (21).

These restrictive regulations that incorporate a narrow range of potential benefits to prisoners as a group or as individuals arise from the concern that prisoners represent a vulnerable population requiring special protections (8). Indeed, there are concerns that research may specifically target the prison population simply out of convenience to the investigators or that the offer to prisoners to participate in research may be coercive or may create an undue influence in favor of participation (22). Given these restrictive regulations, it is conceivable that many of the IRBs concluded that the types of permissible research on prisoners specified in the regulations were not applicable to the ventilator trial. Alternatively, several of the IRBs may not have permitted prisoner participation because they tend not to serve a prison population and therefore lack having a prisoner representative as an IRB member when such research involving prisoners is reviewed, as required by federal regulations (23). In contrast, those IRBs that allowed enrollment of prisoners might have considered the ventilator trial to meet the previously mentioned criterion, that is, "(d) research on practices. . .which have the intent and reasonable probability of improving the health or well-being of the subject" (24). This is another aspect of the federal regulations that is open to variable interpretations and, hence, warrants clarification.

We observed consistency among several of the IRBs' research practices. For example, none of the IRBs required disclosure of investigators' financial compensation in the consent forms. The topic of financial disclosure of investigators' compensation in clinical trials has gained visibility, because financial compensation constitutes a potential conflict of interest that could undermine researchers' objectivity (25). Although the basic federal regulations do not specifically require such a disclosure, they allow IRBs to require disclosure of information that "in the IRB's judgment. . .would meaningfully add to the protection of the rights and welfare of subjects" (26). Accordingly, IRBs could require such disclosure in consent forms. Alternatively, IRBs could require clinical investigators to disclose to them any potential financial conflict of interest so that they could determine whether the level of such compensation could endanger the rights or welfare of the subjects. Such a process would complement recently issued Food and Drug Administration regulations requiring financial disclosure by clinical investigators (27).

IRBs were also consistent in their practices regarding allowing family members to serve as proxy decision-makers for subjects. The federal regulations state that "no investigator may involve a human being as a subject in research. . . unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. . ."(28). The phrase "legally authorized representative" may be interpreted narrowly to mean a court-appointed guardian or broadly to include individuals who are authorized under state law or the rules of the institution to serve as proxy decision-makers for clinical decisions. Apparently, the IRBs in this study embraced the latter interpretation, a practice recently recommended by the National Bioethics Advisory Commission (29).

Within a multicenter trial, Institutional Review Boards reviewing a common protocol varied in several of their approved research practices and in the extent to which the basic elements of informed consent were included in their consent forms.

We also observed variability regarding the degree to which certain basic elements of informed consent were included in the consent forms. Exclusion of basic elements of informed consent may not necessarily represent inappropriate omissions. For example, failure to mention the risks associated with ventilation might have been attributable to the consideration that the types of ventilation administered to subjects in both arms of the study represented standard therapies, the risks of which are not usually stated to such critically ill patients. No guidance is given in the federal regulations concerning whether description of the risks of standard care treatments should be mentioned when administered in the context of a research study. Similar reasoning may have accounted for some IRBs not requiring the mention of the risks associated with the blood samples obtained for research purposes, because

blood sampling per se is not an experimental procedure. Finally, the federal regulations do allow IRBs to exclude or alter some of the basic elements based on the same criteria for a waiver of informed consent (15). We have no way of determining whether the IRBs used these criteria to exclude the basic elements. Alternatively, the variability observed with the inclusion of some of the elements may have been attributable to incomplete knowledge of the federal regulations or an inadequate review process (30), as failure to mention the voluntariness of participation or the ability to withdraw represents basic fundamental elements found in several codes of research ethics (3, 31, 32).

Variability also was observed in the reading levels of the consent forms, with the mean reading levels approximately 3 years greater than the mean reading levels of the general population (below the 8th grade) (33–35). Although some research has addressed the issue of appropriate reading levels of consent forms (36), absence of accepted recommendations on reading levels may be a cause of the variability in consent form reading levels. Alternatively, there may have been differences in the methodology and degree with which IRBs assess systematically the reading levels of the consent forms.

Our findings are consistent with a recent study demonstrating variability in the approved practices among 11 IRBs reviewing a common protocol involving adolescents (37). The investigators in this study determined that the interpretation of minimal risk research by local IRBs was variable, was not always consistent with the federal regulations, and led to a difference in their practices regarding parental involvement in informed consent. Variability in the content of informed consent forms and the readability of these forms also has been observed by the Advisory Committee on Human Radiation Experiments in other contemporary studies (14). Finally, the Food and Drug Administration has reported variability in informed consent forms (4).

The results of our evaluation on the practices of IRBs may not be generalizable to other study situations. Specifically, the type and extent of variations may depend on the type of study (e.g., type of interventions, level of risk), the existence of local factors, and the type of IRBs reviewing the common protocol (e.g., independent, academic, or community). Another limitation to our observations is the modest number of IRBs participating in our study, because use of a much larger sample of IRBs might have indicated more accurately the extent of variability in approved research practices and consent forms. Another consideration is that the variability we observed in the approved research practices might have been attributable in part to variations in investigators' requests to their IRBs concerning the permissibility of prisoner participation, allowance of telephone consent, and the permissibility of a consent waiver. Our analysis was also dependent on survey-reported information from the IRBs rather than a review of the IRBs' meeting minutes documenting the basis of their decisions and policies. Finally, our study is somewhat limited by the subjectivity inherent in assessing the language used to describe some of the basic elements of informed consent.

The existence of variable research practices among IRBs is not inherently a cause for concern if it is attributable to differences in local factors (e.g., absence of a prisoner representative on the IRB, because a prison population is not served by the institution). Our analysis suggests that some of the observed variability might have been attributable to differences in the interpretation of the federal regulations. Accordingly, if these differences are deemed to represent a substantial deviation from the original intent of the federal regulations, then more clarification from the Office for Human Research Protections, the agency responsible for ensuring compliance with the federal regulations, is warranted on the ambiguous aspects of the regulations that may have contributed to the variability in IRB practices noted in this study. Alternatively, variability may have resulted from the differences in the level of scrutiny the IRBs gave to their review process. A recent report of the Department Health and Human Services–Office of the Inspector General (4) stated that IRBs are overworked, understaffed, and underfunded. The Office of the Inspector General report also expressed concern with the adequacy of the knowledge of IRB members, which also may have been a source of variations among the IRBs in this study. As such, further educational efforts for IRB members are warranted, a recommendation made in the Office of the Inspector General report.

In addition to clarification of the federal regulations and educational efforts to reduce unwarranted variations among IRBs, policymakers might consider subjecting multicenter clinical trials to a single "central" review, with each participating institution given the option to accept that approval instead of its own IRB review, make modifications of the central review to ensure that the conduct of the research is responsive to any local factors (e.g., patient recruitment policies), or retain the right to conduct its own comprehensive assessment (19). The central review could be performed at one of the participating institutions or through the National Institutes of Health and could consist of a review of the scientific aspects of the clinical trial, the wording of the informed consent documents, and coordination and oversight of the research practices of the participating institutions. A central review also might enhance the efficiency of the review of research conducted at multiple institutions, thereby reducing the increased workloads of local IRBs attributable to the rapid proliferation of multicenter trials. A pilot effort to assess the efficacy of a central IRB review mechanism is underway at the National Cancer Institute (J. Killen, Chair, National Cancer Institute, Central Institutional Review Board, personal oral and written communication, May 31, 2000). The NHLBI–ARDS Network now requires its ethics committee to review all IRB-approved consent forms to ensure the presence of all basic elements of informed consent. Any efforts at centralized review ought to be evaluated closely to ensure that research subjects are adequately protected.

It is essential to recognize that the IRB system was developed to accommodate research common at that time, a single investigator conducting research in a single institution. Now, much research involves multiple investigators at multiple centers. Accordingly, appropriate changes could lead to less unwarranted variations among different IRBs while simultaneously ensuring the protection of human subjects.

REFERENCES

1. 45 CFR 46: Protection of Human Subjects. Rev. June 18, 1991
2. 21 CFR 50 and 56: Protection of Human Subjects and Institutional Review Boards. Rev. Aug 19, 1991
3. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection

of Human Subjects of Research: Federal Register Document 79-12065; April 18, 1978
4. Institutional Review Boards: Their Role in Reviewing Approved Research. Washington, DC, Office of the Inspector General, June 11, 1998
5. Acute Respiratory Distress Syndrome Clinical Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
6. 45 CFR 46:116(a). Protection of Human Subjects. Rev. June 18, 1991
7. Vanderpool HY: The Ethics of Research Involving Human Subjects: Facing the 21st Century. Frederick, MD, University Publishing Group, 1996
8. Moreno J: Convenient and captive populations. *In:* Beyond Consent: Seeking Justice in Research. Kahn J, Mastroianni A, Sugarman J (Eds). New York, Oxford University Press, 1998, pp 111–130
9. Spece R Jr, Shimm D, Buchanan A: Conflicts of Interest in Clinical Practice and Research. New York: Oxford University Press, 1996
10. Matot I, Pizov R, Sprung C: Evaluation of institutional review board review and informed consent in publications of human research in critical care medicine. *Crit Care Med* 1998; 26:1596–1602
11. Sieber J: Ethical considerations in planning and conducting research on human subjects. *Acad Med* 1993; 68(Suppl 3):S9–S13
12. Brett A, Grodin M: Ethical aspects of human experimentation in health services research. *JAMA* 1991; 265:1854–1857
13. Medical College of Wisconsin IRB Discussion Forum. Available at: http://www.mcwirb.org. Accessed June, 1997
14. Advisory Committee on Human Radiation Experiments: The Human Radiation Experiments. New York: Oxford University Press, 1996
15. 45 CFR 46:116(d). Protection of Human Subjects. Rev. June 18, 1991
16. 45 CRF 46:102(i). Protection of Human Subjects. Rev. June 18, 1991
17. Kopelman LM: When is the risk minimal enough for children to be research subjects? *In:* Children and Health Care: Moral and Social Issues. Kopelman LM, Moskop JL (Eds). Boston, Kluwer Academic, 1989, pp 89–99
18. 45 CFR 46:117(a). Protection of Human Subjects. Rev. June 18, 1991
19. 45 CFR 46:117(b)(2). Protection of Human Subjects. Rev. June 18, 1991
20. 45 CFR 46:117(c). Protection of Human Subjects. Rev. June 18, 1991
21. 45 CFR 46:306. Protection of Human Subjects. Subpart C—Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects. Rev. June 18, 1991
22. Levine R: Ethics and Regulation of Clinical Research. Second Edition. New Haven, CT, Yale University Press, 1986
23. 45 CFR 46:304. Protection of Human Subjects. Subpart C—Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects. Rev. June 18, 1991
24. 45 CFR 46:306 (a)(2)(D). Protection of Human Subjects. Subpart C—Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects. Rev. June 18, 1991
25. Moreno J, Caplan A, Wolpe P, et al: Updating protections for human subjects involved in research. *JAMA* 1998; 280:1951–1958
26. 45 CFR 46:109(b). Institutional Review Boards. Rev. Jan. 27, 1981
27. 21 CFR 54: Financial Disclosure by Clinical Investigators. April 1, 1999
28. 45 CFR 46:116. Protection of Human Subjects. Department of Health and Human Services. Rev. June 18, 1991
29. Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity. Washington DC, National Bioethics Advisory Commission, December 1998
30. U.S. General Accounting Office: Scientific Research: Continued Vigilance Critical to Protecting Human Subjects. Publication FAO/HEHS-96-72. Washington, DC, U.S. General Accounting Office, March 1996
31. Permissible medical experiments. *In:* Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10, October 1946–April 1949, Nuremberg. Washington, DC, U.S. Government Printing Office, October 1946–April 1949, pp 181–182
32. Declaration of Helsinki: *In:* Encyclopedia of Bioethics. New York, Macmillan Publishing, 1995, pp 2765–2767
33. Cooley M, Moriarty H, Berger M, et al: Patient literacy and the readability of written cancer educational materials. *Oncol Nurs Forum* 1995; 22:1345–1351
34. Davis T, Crouch M, Wills G, et al: The gap between patient reading comprehension and the readability of patient education materials. *J Fam Pract* 1990; 31:533–538
35. Powers R: Emergency department patient literacy and the readability of patient-directed materials. *Ann Emerg Med* 1988; 17:124–126
36. Davis T, Holcombe R, Berkel H, et al: Informed consent for clinical trials: A comparative study of standard versus simplified forms. *J Natl Cancer Inst* 1998; 90:668–674
37. Rogers A, Schwartz D, Weissman G, et al: A case study in adolescent participation in clinical research: Eleven clinical sites, one common protocol, and eleven IRBs. *IRB* 1999; 21:6–10